Syllabus **(Updated 1/3/2014)**
Topics in Clinical Trials
Spring Semester 2014
Rice University course STAT 630
University of Texas GSBS course GS01 0813

Time: 8:00 – 9:15 a.m., Tuesday and Thursday
Location: ? Rice University (to be updated)

Instructors:
Peter F. Thall, PhD (rex@mdanderson.org, 713-794-4162)
Brian P. Hobbs, PhD (bphobbs@mdanderson.org, 713-794-4633)

Class Web Site: ?

Prerequisites:
STAT 410: INTRODUCTION TO REGRESSION AND STATISTICAL COMPUTING
STAT 431: OVERVIEW OF MATHEMATICAL STATISTICS

Lecture Schedule

January	February	March	April	May
	4 6	~~4 6~~ (Rice Holidays)	1 3	1
14 16	11 ~~13~~	~~11 13~~ (GSBS Holidays)	8 10	
21 23	18 20	18 20	15 17	
28 30	25 27	25 27	22 24	
			29	

1/14: Hobbs	3/18: Guest lecturer
1/16: Hobbs	3/20: Thall
1/21: Hobbs	3/25: Thall
1/23: Hobbs	3/27: Thall
1/28: Hobbs	4/1: Thall
1/30: Hobbs	4/3: Thall
2/4: Hobbs	4/8: Thall
2/6: Hobbs	4/10: Thall
2/11: Hobbs	4/15: Thall
2/13: Bayesian Biostat Conference, no class	4/17: Guest lecturer
2/18: Hobbs	4/22: Thall
2/20: Hobbs	4/24: Thall
2/25: Hobbs	4/29: Thall
2/27: Hobbs	5/1: Hobbs

Reference Books

1. Cook TD, Demets DL (Ed.) Introduction to Statistical Methods for Clinical Trials. Chapman & Hall/CRC, 2008.
2. Friedman, Furberg, and DeMets: Fundamentals of Clinical Trials. 4th ed.: New York: Springer, 2010
3. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. John Wiley & Sons, 2004.

The lecture topics listed below will be covered as time permits. Students are advised that it is very unlikely that all topics listed below will be covered. Additionally, the topics may not be covered in the order given.

Lecture Topics for Dr. Hobbs

1. Introduction to clinical trials, basic principles
2. Commonly used study designs
3. Randomization and study blindness
4. Outcome adaptive randomization
5. Sample size and power calculation
6. Group sequential designs
7. Interim data monitoring, data safety and monitoring board
8. Meta-analysis and study reporting
9. Phase I – traditional design and the continuous reassessment method (CRM)
10. Phase II – single arm designs, one-stage and multi-stage designs, designs based on predictive probability and Bayes factors
11. Phase II – randomized designs, Bayesian adaptive randomization designs
12. Commensurate priors and historical data in randomized comparative trials

Lecture Topics for Dr. Thall

1. Monitoring a single outcome in phase II clinical trials
   a) Beta-binomial models and methods for binary outcomes [1]
   b) Exponential -gamma models and methods for event times [2]
2. Monitoring multiple outcomes in phase II clinical trials: A Dirichlet-multinomial model-based approach [3,4]
3. Dealing with patient heterogeneity in phase II clinical trials
   a) Bayesian methods based on analysis of variance models [5]
   b) Methods based on Bayesian hierarchical models [6]
4. Phase I-II dose-finding based on efficacy-toxicity trade-offs
   a) The homogeneous case: Trinary and bivariate binary outcomes [7-9]
   b) Individualized dose-finding incorporating covariates [10]
5. Dose-finding with two agents [11]
6. Dealing with multiple toxicities in phase I using total toxicity burden [12]
7. Utility-based dose-finding
   a) Models and methods for two agents with bivariate ordinal efficacy-toxicity outcomes [13]
   b) Optimizing rapid treatment of acute ischemic stroke [14]
8. Hybrid designs
   a) Optimizing dose and schedule [15-17]
   b) Optimizing infusion times [18]
   c) Phase II/III select-and-test designs
      i. Binary outcomes [19]

ii. Event time outcomes [20]
iii. Progression-free-survival time and toxicity [21]

d) Seamless phase II/III designs based on early outcomes and survival time [22]

9. Prior effective sample size in Bayesian clinical trial design [29-31]
10. Dynamic treatment regimes and multi-stage therapies
    a) General concepts [34]
    b) Estimation methods that correct for bias in non-randomized data [33]
    c) A prostate cancer trial of 12 two-stage regimes: Design and analysis [23-25]
    d) A metastatic renal cancer trial of 6 two-stage regimes [26]
    e) Two-stage treatment regimes for acute leukemia [27, 32]
11. Bayesian sensitivity analysis for treatment comparisons based on nonrandomized data [28]

References for Professor Thall's Lectures

1. Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* 50: 337-349, 1994.
2. Thall PF, Wooten LH, Tannir N. Monitoring event times in early phase clinical trials: some practical issues. *Clinical Trials.* 2:467-478, 2005.
3. Thall PF, Simon R, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat in *Medicine* 14:357-379, 1995.
4. Thall PF, Sung H-G. Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Stat in Medicine*, 17:1563-1580, 1998
5. Wathen JK, Thall PF, Cook, JD, Estey EH. Accounting for patient heterogeneity in phase II clinical trials. *Stat in Medicine*. 27:2802-2815, 2008.
6. Thall PF, Wathen JK, Bekele BN, Champlin RE, Baker LO, Benjamin RS. Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. *Stat in Medicine*, 22: 763-780, 2003.
7. Thall PF, Russell KT. A strategy for dose finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. *Biometrics* 54:251-264, 1998.
8. Thall PF, Cook JD. Dose-finding based on efficacy-toxicity trade-offs. Biometrics, 60:684-693, 2004.
9. Thall PF, Cook JD, Estey EH. Adaptive dose selection using efficacy-toxicity trade-offs: illustrations and practical considerations. *J Biopharmaceutical Stat*. 16:623-638, 2006.
10. Thall PF, Nguyen H, Estey EH. Patient-specific dose-finding based on bivariate outcomes and covariates. *Biometrics.* 64:1126-1136, 2008.
11. Thall PF, Millikan RE, Mueller P, Lee S-J. Dose-finding with two agents in phase I oncology trials. *Biometrics*, 59:487-496, 2003.
12. Bekele BN, Thall PF. Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. *J American Statistical Association,* 99:26-35, 2004.
13. Houede N, Thall PF, Nguyen H, Paoletti X, Kramar A. Utility-based optimization of combination therapy using ordinal toxicity and efficacy in phase I/II trials. *Biometrics*. 66:532-540, 2010.
14. Thall PF, Szabo A, Nguyen HQ, Amlie-Lefond CM, Zaidat OO. Optimizing the concentration and bolus of a drug delivered by continuous infusion. *Biometrics*. 67:1638-1646, 2011.
15. Braun TM, Yuan Z, Thall PF. Determining a maximum tolerated schedule of a cytotoxic agent. *Biometrics,* 61:335-343, 2005.
16. Braun TM, Thall PF, Nguyen H, de Lima M. Simultaneously optimizing dose and schedule of a new cytotoxic agent. *Clinical Trials*, 4:113-124, 2007.
17. de Lima M, Giralt S, Thall PF**,** Silva LP, Wang X, Jones RB, Komanduri K, Braun TM**,** Nguyen HQ**,** Champlin R, Garcia-Manero G. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for relapsed AML or MDS: a dose and schedule finding study. *Cancer.* 116:5420-5431, 2010.
18. Thall PF, Inoue LYT, Martin T. Adaptive decision making in a lymphocyte infusion trial. *Biometrics*, 58:560-568, 2002.
19. Thall PF, Simon R, Ellenberg SS. Two-stage selection and testing designs for comparative clinical trials. Biometrika 75: 303-310, 1988.

20. Schaid DJ, Wieand HS, Therneau TM. Optimal two-stage screening designs for survival comparisons. *Biometrika* 77: 507-513. 1990.
21. Thall PF, Nguyen HQ, Wang X, Wolff JE. A hybrid geometric phase II/III clinical trial design based on treatment failure time and toxicity. *J Statistical Planning and Inference*. 142:944-955, 2012.
22. Inoue LYT, Thall PF, Berry, DA. Seamlessly expanding a randomized phase II trial to phase III. *Biometrics*, 58:823-831, 2002.
23. Thall PF, Millikan R, Sung, H-G. Evaluating multiple treatment courses in clinical trials. *Stat in Medicine*, 19: 1011-1028, 2000
24. Thall PF, Logothetis C, Pagliaro L, Wen S, Brown MA, Williams D, Millikan R. Adaptive therapy for androgen independent prostate cancer: A randomized selection trial including four regimens. *J National Cancer Institute*. 99:1613-1622, 2007
25. Wang L, Rotnitzky A, Lin X, Millikan R, Thall PF. Evaluation of viable dynamic treatment regimes in a sequentially randomized trial of advanced prostate cancer. *J. American Statistical Association*. In press.
26. Thall PF, Wooten LH, Logothetis CJ, Millikan R, Tannir NM. Bayesian and frequentist two-stage treatment strategies based on sequential failure times subject to interval censoring. *Stat in Medicine*. 26:4687-4702, 2007.
27. Thall PF, Sung H-G, Estey EH. Selecting therapeutic strategies based on efficacy and death in multi-course clinical trials. *J American Statistical Association*, 97:29-39, 2002.
28. Thall PF, Champlin RE, Andersson BE. Comparison of 100-day mortality rates associated with IV busulfan and cyclophosphamide versus other preparative regimens in allogeneic bone marrow transplant for chronic myelogenous leukemia: Bayesian sensitivity analyses of confounded treatment and center effects. *Bone Marrow Transplantation*, 33: 1191-1199, 2004.
29. Morita S, Thall PF, Mueller P. Determining the effective sample size of a parametric prior. Biometrics. 64:595-602, 2008.
30. Morita S, Thall PF, Mueller P. Evaluating the impact of prior assumptions in Bayesian biostatistics. Statistics in Biosciences. 2:1-17, 2010.
31. Morita S, Thall PF, Mueller P. Prior effective sample size in conditionally independent hierarchical models. Bayesian Analysis. 7:591-614, 2012
32. Wahed AS, Thall PF. Evaluating joint effects of induction-salvage treatment regimes on overall survival in acute leukemia. J Royal Statistical Society, Series C (Applied Statistics). 62:67-83, 2013.
33. Hernan, M.A., Brumback, B. and Robins, J.M. Marginal structural models to estimate the causal effect of Zidovudine on the survival of HIV-positive men. Epidemiology. 11:561-570, 2000.
34. Moodie, E.E.M, Richardson, T.S. and Stephens, D.A. Demystifying optimal dynamic treatment regimes. Biometrics. 63:447-455, 2007.